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Determination of Conditions for the Production Scale Sterilization of Prefilled Syringes

NORIHIRO NISHIMOTO[1]* and TATSUYUKI MAEKAWA[2]

[1]*Osaka Pharmaceutical Research Center, Daiichi Pharmaceutical Co. Ltd.* [2]*Tokyo Pharmaceutical Research Center, Daiichi Pharmaceutical Co. Ltd.*

ABSTRACT: External and internal differences in pressure of prefilled syringes can cause plunger movement during sterilization, which might cause drug product contamination. Consequently the pressure inside the autoclave during sterilization should be controlled carefully to prevent contamination of the drug product by microorganism and particulates. A previously determined theoretical relationship of temperature to pressure in sealed bottles was modified for prefilled syringes to take plunger movement into account. This modification yielded a correction factor that includes a coefficient of linear thermal expansion for the syringe, thermal expansion of the plunger, and friction between the plunger and the syringe wall. To confirm the accuracy of this modified relationship, 100 mL polypropylene prefilled syringes with butyl rubber plungers, some of which carried pressure and temperature sensors, were used to test various sterilization conditions at the experimental scale. The results showed that the major problem in establishing the pressure conditions for production scale sterilization is temperature distribution throughout the load. However, an over pressure sterilization cycle at 121°C and 0.34 MPa showed the best results. Microbial challenge and light-obscuration particle count tests were performed on the syringes from the worst-case location predicted from modified relationship; the results show that these conditions preserved the sterility of the drug product and protected it from particulate contamination.

Introduction

Sterile parenteral drug products should be terminally sterilized by heating in their final container if terminal sterilization does not causes unacceptable degradation of the products, or if terminal sterilization deprives substantial clinical advantage of market presentation (1, 2). Recently, many parenteral drugs have begun being marketed in plastic containers. Unlike previously used packaging materials such as glass or metal, plastic can expand or deform under high temperature and pressure conditions such as those seem during autoclave sterilization. Thus, controlling the chamber pressure during the sterilization cycle is important to prevent deformation or breakage of such containers. This is especially true for prefilled syringes because the plunger is not fixed; if the chamber pressure is not adequately controlled, the plunger might be displaced or move significantly outward, which might lead to microbial and particulate contamination of the packaged drug product. While high pressure might prevent this, an excessively high pressure might cause the container to deform or to break. Unfortunately, while much is known about optimizing sterilization conditions for glass and metal containers (3), little information has been reported on optimum conditions for prefilled syringe sterilization. Consequently, this study was conducted to determine optimum conditions for these drug presentations.

R. E. Beck derived an internal pressure-temperature relationship for autoclave sterilization of solutions in sealed bottles from five events postulated to occur as the container is heated:

1. Water evaporates into the headspace.
2. The liquid phase expands as temperature increases.
3. The vapor phase attempts to expand as the temperature increases.

*Author to whom correspondence should be addressed: Daiichi Pharmaceutical Co., Ltd., Osaka Pharmaceutical Research Center, 4-38, Aketa-cho, Takatsuki-shi, Osaka 569-0806, Japan. Phone: +81-72-685-2836. Fax: +81-72-682-8975. E-mail: nishi5og@daiichipharm.co.jp

4. Dissolved gases vaporize and enter the headspace.

5. The container walls expand reversibly to increase the total volume of the container.

This theoretical relationship of temperature to pressure was defined from the vapor pressure, density, and Henry's Law constant of the solution; and the coefficient of linear thermal expansion of the container (4, 5). A subsequent experiment confirmed the validity of this relationship (6). The derivation of the following equation, which expresses these relationships, is given in References 4 and 5.

$$P = P_{vp} + (P_0 - P_{vp0}) \times \left(\frac{1 + \frac{H_0 MW_w}{R\rho_{w0}T_0}\left(\frac{Y_0}{1-Y_0}\right)}{\frac{H_0 MW_w}{R\rho_{w0}T}\left\{\frac{[1+C(T-T_0)]^3}{(1-Y_0)} - \frac{\rho_{w0}}{\rho_w}\right\} + \frac{H_0}{H}} \right) \quad (1)$$

Unfortunately, this equation is applicable only for fixed-stopper containers, vials, bottles, plastic bags, and others. However, in a prefilled syringe, the plunger can move during sterilization; consequently, plunger motion must be considered to estimate the internal pressure precisely. An increase in volume within the syringe cylinder caused by this motion adds to the fifth event originally considered by Beck. Thus the total volume can be expressed by the following equations:

$$V_c = \{1 + C(T - T_0)\}^3 V_{c0} + U_c V_{c0} \quad (2)$$

$$U_c = \frac{U_m \times S_0}{V_{c0}} \quad (3)$$

Where U_c is the portion of the syringe volume at T caused by the plunger movement from the initial volume, U_m is the distance traveled by plunger, and S is the sectional area of syringe container. Providing that the solution is water and that air occupies the headspace, Equations 2 and 3 can be substituted into the Beck Equation (Eq. 1) to yield:

$$P = P_{vp} + (P_0 - P_{vp0}) \times \left(\frac{1 + \frac{H_0 MW_w}{R\rho_{w0}T_0}\left(\frac{Y_0}{1-Y_0}\right)}{\frac{H_0 MW_w}{R\rho_{w0}T}\left\{\frac{[1+C(T-T_0)]^3 + U_c}{(1-Y_0)} - \frac{\rho_{w0}}{\rho_w}\right\} + \frac{H_0}{H}} \right) \quad (4)$$

where

T = temperature

P = container pressure at T

P_{vp} = vapor pressure of water at T

H = Henry's Law constant for air at T

MW_w = molecular weight of water

R = universal gas constant

ρ_w = density of water

C = coefficient of linear thermal expansion for the container material or correction factor

V_c = total volume of container

Y = fraction occupied by air and water vapor

subscript 0 = conditions when the container is sealed

Values for the vapor pressure, the density, and the Henry's Law constant of the solution—and the coefficient of linear thermal expansion of the container—are needed in order to use Eq. 4 to calculate simulated internal pressure values. In order to perform computer simulation, Beck developed the following equations, which empirically fit tables of reported data for the vapor pressure, density of water, and the solubility of air in water:

$$P_{vp} = e^{(16.0 - 4967/T)} \quad (5)$$

$$\frac{\rho_w}{\rho_{w0}} = 0.84829 + 0.0013128T - (2.713 \times 10^{-6})T^2 \quad (6)$$

$$\frac{H}{H_0} = 1.627 - \frac{223}{T} e^{-[(T-273.2)/45]^2} \quad (7)$$

where $H_0 = 6.64 \times 10^4$ atm at 20°C.

In this study, the vapor pressure, the density, and the Henry's Law constant of water are also used to calculate the internal pressure of syringe presentation filled with drug solution because the drug solution is aqueous.

TABLE I
Syringe Sample

Syringe barrel material	Polypropylene
Plunger material	Butyl rubber
Fill solution	Water for injection or aqueous drug solution
Fill temperature	293.15 K
Fill volume	102 mL
Head space gas	Air
Headspace	2 mL

Although Beck cited only one coefficient of linear thermal expansion for polypropylene (4), there is more than one kind of polypropylene and the coefficient of linear thermal expansion is different for each type (7); consequently, a standard ASTM method (8) was used to measure the coefficient of linear thermal expansion of syringes used in this study. However, the ASTM method should be used for materials that have a very low thermal expansion and should be performed only between −30 and 30°C (8). Therefore, the coefficient of linear thermal expansion for these syringes, determined by using the ASTM method, could not be used in calculations that use high temperature and pressure conditions, such as sterilization. Additionally, it is necessary to take into account the thermal expansion of the plunger and effect of friction on the plunger to predict the internal pressure in the prefilled syringe while the plunger is moving.

To overcome the difficulties in determining the coefficient of linear thermal expansion of the syringe, the thermal expansion of the plunger, and the effect of friction on the plunger during sterilization, a practical method was used to back-calculate the coefficient of linear thermal expansion from Eq. 4 using temperature, pressure, and plunger movement distance; these values could be measured during sterilization cycle. However, it should be noted that the coefficient of linear thermal expansion calculated from this method is not truly a coefficient of linear thermal expansion of the syringe container but a correction factor for this syringe-and-plunger combination to predict the internal pressure, which includes a coefficient of linear thermal expansion of the syringe container, thermal expansion of the plunger, and frictional resistance of the plunger movement.

Materials and Methods

In this study, the optimum pressure conditions to provide in order to prevent contamination or container damage during sterilization were studied using 100 mL syringes with rubber plungers. Table I shows the materials that make up the syringe and the composition of the syringe presentation. After the syringe barrel and plunger were sterilized at 121°C for 20 min, water for injection or an aqueous drug solution was filled at 20°C.

The optimum pressure conditions for production-scale sterilization were established according to the following steps.

1. Eq. 4 was used to determine the correction factor for the syringe and plunger system using temperature, pressure, and plunger movement distance values measured during experimental-scale sterilization tests.

2. The correction factor for syringe and plunger system determined during step 1 was verified on the experimental scale.

3. Eq. 4 was used to determine the pressure conditions for production-scale sterilization using the correction factor determined from experimental-scale sterilization tests.

4. The microbial and particulate quality of syringe presentation sterilized using the production-scale process was evaluated using samples sterilized at the worst-case location.

Autoclaves

The experimental-scale autoclave was a water cascade autoclave, and the production-scale autoclave was fan-mixed air overpressure autoclave (Tables II, III). Figure 1 depicts the experimental-scale sterilization cy-

TABLE II
Experimental-Scale Autoclave

Sterilization Method	Water cascade autoclave
Chamber Size	1,000(diameter) × 1,200(L) mm
Max Pressure	0.49 MPa

TABLE III
Production-Scale Autoclave

Sterilization Method	Fan-mixed air overpressure autoclave
Chamber Size	1,120(W) × 1,800(H) × 3,750(L) mm
Max Pressure	0.40 MPa
Max Load	6048 syringes (100 mL syringe)

cle, and Figure 2 depicts the production-scale sterilization cycle. The experimental autoclave has one heating cycle and one cool-down cycle. The production-scale autoclave has three heating cycles, three cool-down cycles, and one drying cycle. Since the point to be considered was the internal pressure-temperature relationship, the differences in the sterilization method and sterilization cycles were disregarded.

Measuring Internal Pressure, Internal Temperature, and Plunger Movement Distance

Initially, one syringe was outfitted with temperature and pressure sensors to conduct measurement. A pressure logger (EBI-125A-PT, ebro Electric GmbH & Co. KG; Ingolstadt, Germany) was attached on the fitting side, and a T-type thermocouple was inserted through the plunger (Figure 3). Silicone caulking was used to seal the sensors to the syringe. Two syringes were sterilized at the same time to measure internal pressure, temperature, and plunger movement distance. One was fitted with the pressure logger and the thermocouple. The other was fitted with the scale and

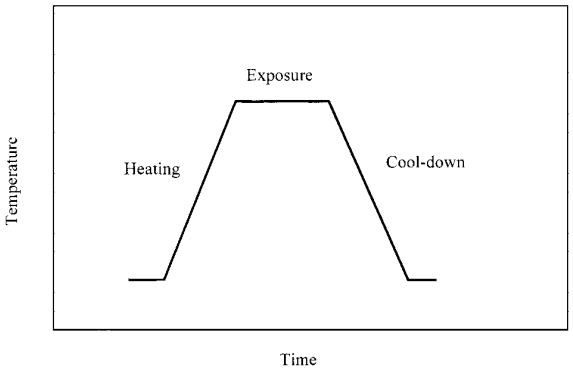

Figure 1

Schematic diagram of the experimental-scale sterilization cycle.

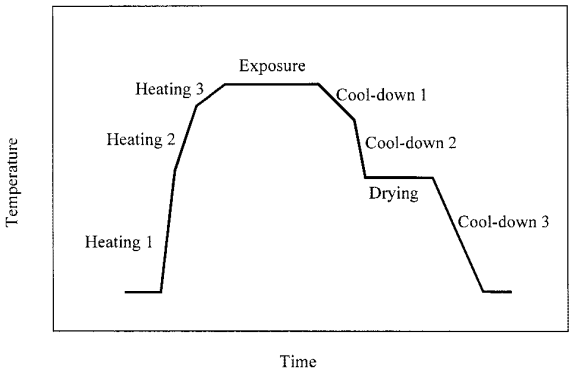

Figure 2

Schematic diagram of the production-scale sterilization cycle.

placed close to the sensor-equipped syringe to measure the plunger movement distance. Pressure and temperature data were collected every 10 s using the pressure logger and the Validator KL (GE Kaye Instruments, Inc.; North Billerica, MA) were analyzed with Excel 95 (Microsoft Corporation; Redmond, WA).

Results and Discussion

Determination of the Correction Factor

The experimental-scale sterilization process was used to determine the correction factor for this syringe and plunger set. The first pressure condition examined was designed to make the plunger move markedly; the coefficient of linear thermal expansion at 20°C measured by the ASTM method was used to set this condition. After the sterilization cycle was finished, the correction factors at each temperature point were back-calculated from Eq. 4 using internal pressure,

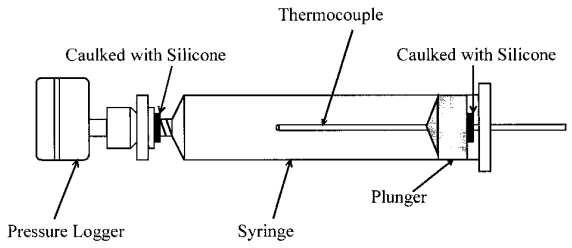

Figure 3

Syringe equipped with pressure and temperature loggers.

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